

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/10181 A1

(51) International Patent Classification⁷: C07H 17/08, A61K 31/7052, A61P 31/04

(21) International Application Number: PCT/IB01/01327

(22) International Filing Date: 25 July 2001 (25.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P-200001934 31 July 2000 (31.07.2000) ES

(71) Applicant (for all designated States except US): QUIM-ICA SINTETICA, S.A. [ES/ES]; C. de l'Acce, 24, E-08004 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BAÑON PARDO, Gabriel [ES/ES]; c/ Río Segura, 20, E-28803 Alcalá de Henares (ES). GONZALES HERNANDEZ, Pedro [ES/ES]; Avda. Reyes Católicos, 3A, 3°C, E-28802 Alcalá de Henares (ES). LOPEZ GARCIA, Julia [ES/ES]; c/ Andrés Mellado, 13, 1°C, E-28015 Madrid (ES). RIAÑO RIBOTA, Ana María [ES/ES]; Avda. del Mediterráneo, 17, E-28007 Madrid (ES). GELPI VINTRO, José María [ES/ES]; Ronda General Mitre, 33, 4°, E-08017 Barcelona (ES). FAU DE CASA-JUANA MUÑOZ, Miquel [ES/ES]; c/ Guaimaral, 4, 2° derecha, E-28033 Madrid (ES).

(74) Agents: PONTI SALES, Adelaida et al.; C. Consell de Cent, 322, E-08007 Barcelona (ES).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AZITHROMOCIN MONOHYDRATE WITH LOWER HYGROSCOPICITY, PREPARATION METHOD AND PHARMACEUTICAL COMPOSITIONS WHICH INCLUDE IT

(57) Abstract: The improved form of azitromycin monohydrate of lower hygroscopicity and greater density and hardness that presents values of: apparent filling density not lower than 0.35 g/ml; and apparent knocked density not lower than 0.50 g/ml. The method for preparation of an improved form of azitromycin monohydrate is characterised in that the hygroscopic azitromycin monohydrate is subjected to a procession of compaction by pressure. The invention also refers to a pharmaceutical composition that includes a therapeutically effective quantity of improved form of azitromycin monohydrate in association with at least one pharmaceutically acceptable suitable inert diluent.



WO 02/10181 A1

AZITHROMOCIN MONOHYDRATE WITH LOWER HYGROSCOPICITY, PREPARATION METHOD AND PHARMACEUTICAL COMPOSITIONS WHICH INCLUDE IT

5

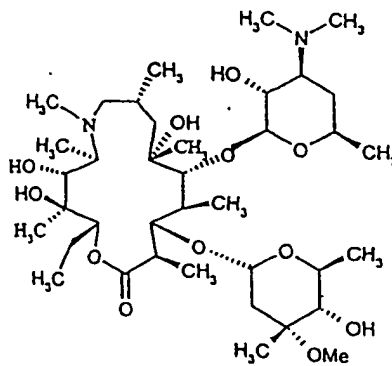
Field of the invention

This invention relates to a new improved form of azitromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin 10 A) monohydrate, the monohydrated form of azitromycin of lower hygroscopicity, the method for making it and the pharmaceutical compositions which include it.

Background of the invention

15

Azithromycin or 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A is a broad-spectrum antibacterial agent that was disclosed and patented by Sour Pliva in Yugoslav priority application YU 000592 of 06.03.81, which priority
20 was invoked in the equivalent American patent US 4517359.



These patents describe the preparation of the product by means of an Eschweiler-Clarke methylation reaction of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

5 Two crystalline forms of azitromycin are known: azitromycin monohydrate and azitromycin dihydrate.

The dihydrated form of azitromycin is obtained by crystallisation of the product in a mixture of
10 tetrahydrofuran and an aliphatic hydrocarbon in the presence of water (EP 298.650) or by means of recrystallisation of the product of aketone and water (*J. Chem. Research (M)*, 1988, 1239-1261; *J. Chem. Research (S)*, 1988, 152-153).

15

Furthermore, the azitromycin monohydrate is prepared by crystallisation of the product from mixtures of ethanol and water (EP 298.650) or aketone and water.

20 Both monohydrated and dihydrated forms are easily distinguishable by their X-ray diffraction spectrums, IR spectrums, differential calorimetry analysis (DSC) and thermogravimetric analysis (TGA).

25 In European patent EP 298.650 from Pfizer, Messrs Allen and Nepveux describe how when azitromycin is obtained according to the Eschweiler-Clark methylation procedure of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A with formaldehyde and formic acid and the azitromycin resulting
30 from ethanol and water is recrystallised, the monohydrated form of azitromycin is obtained. This product is hygroscopic and can be used only with difficulty, since the monohydrate absorbs variable amounts of water, which makes it difficult to use for medicinal formulation.

35

The only method by which Messrs Allen and Nepveux overcame these difficulties and limitations of the monohydrated form of azitromycin was by developing a new form of azitromycin, the dihydrate of azitromycin, described and
5 claimed in EP 298.650.

Description of the invention

It is, therefore, an object of this invention to provide
10 an improved form of azitromycin monohydrate which overcomes the difficulties and limitations of the hygroscopic azitromycin monohydrate form previously known and which shows lower hygroscopicity.

15 The term "an improved form of azitromycin monohydrate" can alternatively be denominated "azitromycin monohydrate of the invention". These terms are used interchangeably in this specification.

20 The term "hygroscopic azitromycin monohydrate" refers to the azitromycin monohydrate previously known through EP298650. More specifically, it refers to the azitromycin monohydrate described on page 4, lines 25-48 of EP298650.

25 This "hygroscopic azitromycin monohydrate" is the reference molecule of this invention. In consequence, when for example in the invention "an improved form of azitromycin monohydrate that presents lower hygroscopicity" is used, this "lower hygroscopicity"
30 refers to lower hygroscopicity when compared with the hygroscopicity of the reference molecule "hygroscopic azitromycin monohydrate" reference molecule of EP298650. The same is the case when the statement "denser and stronger" is used in relation to the azitromycin of the

invention, that is, it is "denser" when compared with the reference molecule of EP298650.

Another object of this invention is to disclose a method of preparation of an improved form of monohydrated azitromycin of lower hygroscopicity, which method provides the improved form of monohydrated azitromycin with a practically constant water content and in a reproducible manner.

10

Another object of this invention is to disclose pharmaceutical compositions which include an improved form of azitromycin monohydrate, the monohydrated azitromycin of lower hygroscopicity.

15

In accordance with one of the objects of this invention, a new form of azitromycin monohydrate has been surprisingly discovered, a form which overcomes the difficulties and limitations of the previously known form of azitromycin monohydrate and which presents lower hygroscopicity, this improved form being a compound of lower hygroscopicity which has apparent density values that are especially suitable for its use as an active ingredient in the formulation of tablets and other medicinal forms.

25

The improved form of azitromycin monohydrate of lower hygroscopicity is characterised in that it is denser and stronger and possesses values of:

- apparent filling density not lower than 0.35 g/ml, preferably not lower than 0.40 g/ml, and more preferably still not lower than 0.45 g/ml, and still more preferably not lower than 0.50 g/ml and yet more preferably not lower than 0.53 g/ml; and

- apparent knocked density not lower than 0.50 g/ml, preferably not lower than 0.55 g/ml, and more preferably still not lower than 0.60 g/ml, and still more preferably not lower than 0.65 g/ml and yet more preferably not lower than 0.70 g/ml.

Preferably, the "apparent filling density" is measured by weighing out approximately 100 g of product measured with a precision of 0.1%. If it is not possible to use 100 g, the quantity of sample and the volume of the cylinder and the conditions specified in the analysis can be altered. A quantity of sample is selected such that it has an apparent loose volume of 150 to 250 ml. The uncompacted powder is then transferred carefully to a dry graduated cylinder of 250 ml (graduated cylinder weight: 220 ± 44 g), by sliding the product gently. The apparent unsedimented volume occupied by the sample is then read, and it is approximated to the closest graduated unit: Volume (1) (expressed in ml), and the apparent filling density calculated using the formula:

Apparent filling density = weight of sample (g)/V(1) ml.
This procedure is that of USP24, Test 616.

Preferably, the apparent knocked density is measured in a Pharma Test apparatus (model PT-TD), with a knocking speed of 250 ± 10 blows/minute and a knocking height of 3 ± 0.1 mm, securing the cylinder in the bracket of the equipment and knocking initially 500 times. The volume occupied by the sample is noted and approximated to the nearest graduation of the graduated cylinder. This is the volume (2). The sample is then given a further 750 knocks and the knocked volume occupied by the sample measured: Volume (3). If the difference between the two volumes $[V(3) - V(2)]$ is less than 2%, V(3) is the final volume for calculating the

apparent knocked density. If the difference is greater than 2%, then knocking of the sample in increments of 1250 blows each time is continued until consecutive readings with a difference of less than 2% between them are 5 obtained. The knocked density in g/ml is calculated using the following formula:

Apparent knocked density = weight of sample (g)/V(3) ml.
This procedure is that of USP24, Test 616.

10

The technical characteristic of the density of the azitromycin monohydrate of the invention provides the effect of lower hygroscopicity. The object of this invention, as mentioned above, can therefore be expressed 15 alternatively as: a azitromycin monohydrate which is characterised in that it possesses values of:

- apparent filling density not lower than those mentioned previously; and
- apparent knocked density not lower than those 20 mentioned previously.

The improved form of azitromycin monohydrate of lower hygroscopicity is further characterised in that it presents an initial water content of between 3.2% and 25 3.6%, a water gain of between 0.16 and 0.23% at 24 hours and between 0.3 and 0.51% at four days, finally stabilising at a water content of 3.6 to 3.9%, under ambient humidity conditions of between 20 and 40% and at temperatures in the range 20-30°C.

30

The azitromycin monohydrate presents apparent filling density values not exceeding 0.29 g/ml and apparent knocked density values not exceeding 0.44 g/ml.

Moreover, if the hygroscopic azitromycin monohydrate is exposed to the atmosphere and maintained under mean ambient conditions of 20-30°C of temperature and 20-40% of ambient relative humidity, it presents a water gain of 5 1.2% at 24 hours and of 1.3% at four days, finally stabilising at a water content of 4.6%.

The X-ray diffraction spectrum of the improved form of azitromycin monohydrate of lower hygroscopicity shows that 10 the product presents a lower crystalline content when compared with that of the hygroscopic azitromycin monohydrate, which can have a positive effect in improvements in its solubility and bioavailability.

15 Furthermore, the values for melting point, DSC and IR spectrum of the new improved form of azitromycin monohydrate of lower hygroscopicity are identical to those of the hygroscopic azitromycin monohydrate.

20 In accordance with another aspect of this invention, a method is disclosed for preparation of an improved form of azitromycin monohydrate, the azitromycin monohydrate of lower hygroscopicity, which method gives rise surprisingly to an improved form of azitromycin monohydrate with a 25 practically constant water content and in a reproducible manner.

The hygroscopic azitromycin monohydrate is obtained by means of an Eschweiler-Clarke reaction of the 9-deoxo-9a- 30 aza-9a-methyl-9a-homoerythromycin A with formaldehyde and formic acid, the resulting product being recrystallised in mixtures of ethanol and water or of acetone and water to provide the hygroscopic monohydrate form.

The method for preparing an improved form of azitromycin monohydrate, the azitromycin monohydrate of lower hygroscopicity, is characterised in that the hygroscopic azitromycin monohydrate is subjected to a procession of 5 compaction by pressure.

The hygroscopic azitromycin monohydrate can be obtained via the reaction based on Eschweiler-Clark described above. However, it is possible to obtain it by different 10 protocols in accordance with the general state of the art on the subject. The characteristic feature of the method of the invention is that the hygroscopic azitromycin monohydrate is submitted to a process of compaction by pressure. The specific method used for obtaining the 15 hygroscopic azitromycin monohydrate is not essential in nature, although the preferred procedure is that mentioned previously.

The compaction pressure can range between 50 and 200 20 kg/cm², but is preferably between 100 and 200 kg/cm².

The speed of rotation of the rollers has to be between 5 and 15 rpm, and is preferably between 9 and 15 rpm.

25 The mesh size has to be between 0.5 and 2 mm, preferably with an opening size of between 1 and 2 mm.

Any type of compactor can be used, though preferably a roller compactor.

30

In accordance with the method object of this invention, it has been found that when the hygroscopic azitromycin monohydrate is subjected to a process of compaction by pressure resulting in a product of greater apparent 35 density, this new product surprisingly presents the

advantageous property of possessing a lower tendency to take up water contained in the atmosphere, the characteristic of lower hygroscopicity.

5 This new improved form of azitromycin monohydrate of lower hygroscopicity remains stable during and after the process of compaction by pressure, without there taking place any increase in the level of impurities in the resulting product.

10

In accordance with the method of this invention, it has surprisingly proved possible to obtain a product which, if exposed to the atmosphere and kept at mean ambient conditions of 20-30°C of temperature and 20-40% of ambient
15 relative humidity, presents a water gain of 0.23% at 24 hours and of 0.513% at four days, finally stabilising at a water content value of 3.9%, while the uncompacted hygroscopic azitromycin monohydrate presents a water gain of 1.2% and 1.3%, respectively, at the end of said periods
20 of time, finally stabilising at a water content of 4.6%.

The efficacy of the method in this respect was confirmed by the fact when the same product is submitted to a double operation of compaction by means of pressure, the water
25 gain after 24 hours and 4 days is 0.16% and 0.30%, respectively, leaving the product finally stabilised at a water content of 3.6%.

Another object of this invention relates to the
30 pharmaceutical composition that include a therapeutically effective quantity of azitromycin monohydrate of lower hygroscopicity in association with at least one pharmaceutically acceptable suitable inert diluent.

The pharmaceutical composition in accordance with this invention can be prepared by combining the azitromycin monohydrate of lower hygroscopicity with at least one pharmaceutically acceptable suitable inert diluent and 5 administering it orally and parenterally.

This invention is illustrated by means of the following examples. It should nevertheless be understood that this invention is not limited to the specific examples in them.

10

Drawings

Figure 1 shows the X-ray spectrum of hygroscopic azitromycin monohydrate.

15

Figure 2 shows the X-ray diffractogram of the improved form of azitromycin monohydrate.

Figure 3 shows the IR spectrum of the hygroscopic 20 azitromycin monohydrate.

Figure 4 shows the IR spectrum of the improved form of azitromycin monohydrate of lower hygroscopicity.

25 Examples

Example 1 to 5

20 Kg of hygroscopic azitromycin monohydrate having 30 filling density values of 0.29 g/ml and knocked density of 0.44 g/ml were compacted in a roller compactor of the Bonal trademark, model BC-175/75V fitted with screen with 1 mm mesh size, and the compaction pressure and roller rotation speed parameters were set as indicated in Table

A. The density results obtained are shown in the same table.

Table A: Compaction Conditions

5

Example No.	Compaction Pressure (kg/cm ²)	Roller rotation speed (rpm)	Filling Density (g/ml)	Knocked Density (g/ml)
1	75	11.1	0.49	0.61
2	100	11.1	0.51	0.62
3	130	10	0.52	0.64
4	150	10	0.53	0.70
5 (*)	150	10	0.55	0.74

(*) New product compaction value obtained by combining examples 1 and 2.

10

Hygroscopicity results

Table B below shows the comparative hygroscopicity results obtained with the hygroscopic azitromycin monohydrate and the improved form of azitromycin of lower hygroscopicity. Said table shows the changes in the water content of the product over time, measured by the Karl Fischer method, when exposed to the following ambient conditions:

Temperature between: 20-30°C

20 Relative Humidity between: 20-40%

Table B: Hygroscopicity

Time	Hygroscopic azitromycin monohydrate (% H ₂ O)	Product Example 4 (% H ₂ O)	Product Example 5 (% H ₂ O)
0	3.28	3.39	3.33
24 hours	4.49	3.62	3.49
2 days	4.52	3.70	3.53
4 days	4.59	3.90	3.63
15 days	4.6	3.9	3.6

5

Stability results

Table C below shows that the quality of the product remained unchanged after it had been submitted to the 10 compaction process.

Table C: Stability

Parameter	Hygroscopic azitromycin monohydrate	Product Example 4
Specific rotation (s.s.s.)	-48.8°	-47.5°
pH (0.2% solution in methanol/water, 1:1)	9.98	10.1
Purity (%)	98.0	98.2

15

Results of the X-ray diffractograms

The X-ray diffractograms were obtained by means of a Philips Analytical X-Ray B.V. diffractometer of type PW 1710, operating at 40 kV and 40 mA and using a copper radiation of $\lambda_1=1.54056\text{\AA}$ and $\lambda_2=1.54439\text{\AA}$. This equipment has a graphite monochromator with automatic slit, and the crystalline powder method was used.

10

Figure 1 corresponds to the X-ray spectrum of hygroscopic azitromycin monohydrate, while Figure 2 corresponds to the X-ray diffractogram of the improved form of azitromycin monohydrate.

15

A comparison of them shows a reduction of crystallinity in the improved form of azitromycin monohydrate.

20 Infrared spectrum results

Attached below are the IR spectrum results of hygroscopic azitromycin monohydrate and the improved form of azitromycin monohydrate, recorded on a Perkin Elmer 25 spectrometer, model 1600 Series FTIR.

Figure 3 shows the IR spectrum of the hygroscopic azitromycin monohydrate, while Figure 4 shows the IR spectrum of the improved form of azitromycin monohydrate of lower hygroscopicity.

CLAIMS

1. Improved form of azitromycin monohydrate of lower hygroscopicity and greater density and hardness that
5 presents values of:

- apparent filling density not lower than 0.35 g/ml; and
- apparent knocked density not lower than 0.50 g/ml.

10

2. Improved form of azitromycin monohydrate as claimed in Claim 1, which further presents an initial water content of between 3.2% and 3.6%, a water gain of between 0.16 and 0.23% at 24 hours and between 0.30 and
15 0.51% at four days, finally stabilising at a water content of 3.6 to 3.9%, under ambient humidity conditions of between 20 and 40% and at temperatures in the range 20-30°C.

20 3. Improved form of azitromycin monohydrate as claimed in Claim 1, in which the apparent filling density is not less than 0.40 g/ml and apparent knocked density not less than 0.55 g/ml.

25 4. Improved form of azitromycin monohydrate as claimed in Claim 1, in which the apparent filling density is not less than 0.45 g/ml and apparent knocked density not less than 0.60 g/ml.

30 5. Improved form of azitromycin monohydrate as claimed in Claim 1, in which the apparent filling density is not less than 0.50 g/ml and apparent knocked density not less than 0.65 g/ml.

6. Improved form of azitromycin monohydrate as claimed in Claim 1, in which the apparent filling density is not less than 0.53 g/ml and apparent knocked density not less than 0.70 g/ml.

5

7. Method for preparation of an improved form of azitromycin monohydrate as claimed in any of the previous claims, characterised in that the hygroscopic azitromycin monohydrate is subjected to a procession of compaction by
10 pressure.

8. Method as claimed in Claim 7, characterised in that the compaction pressure is furthermore ranges between 50 and 200 kg/cm², the speed of rotation of the rollers is
15 between 5 and 15 rpm and the mesh size is between 0.5 and 2 mm.

9. Method as claimed in Claim 8, characterised in that the compaction pressure is 150 kg/cm², the speed of
20 rotation of the rollers is 10 rpm and the mesh size is 1 mm.

10. Product that can be obtained according to any of method claims 7, 8 or 9.

25

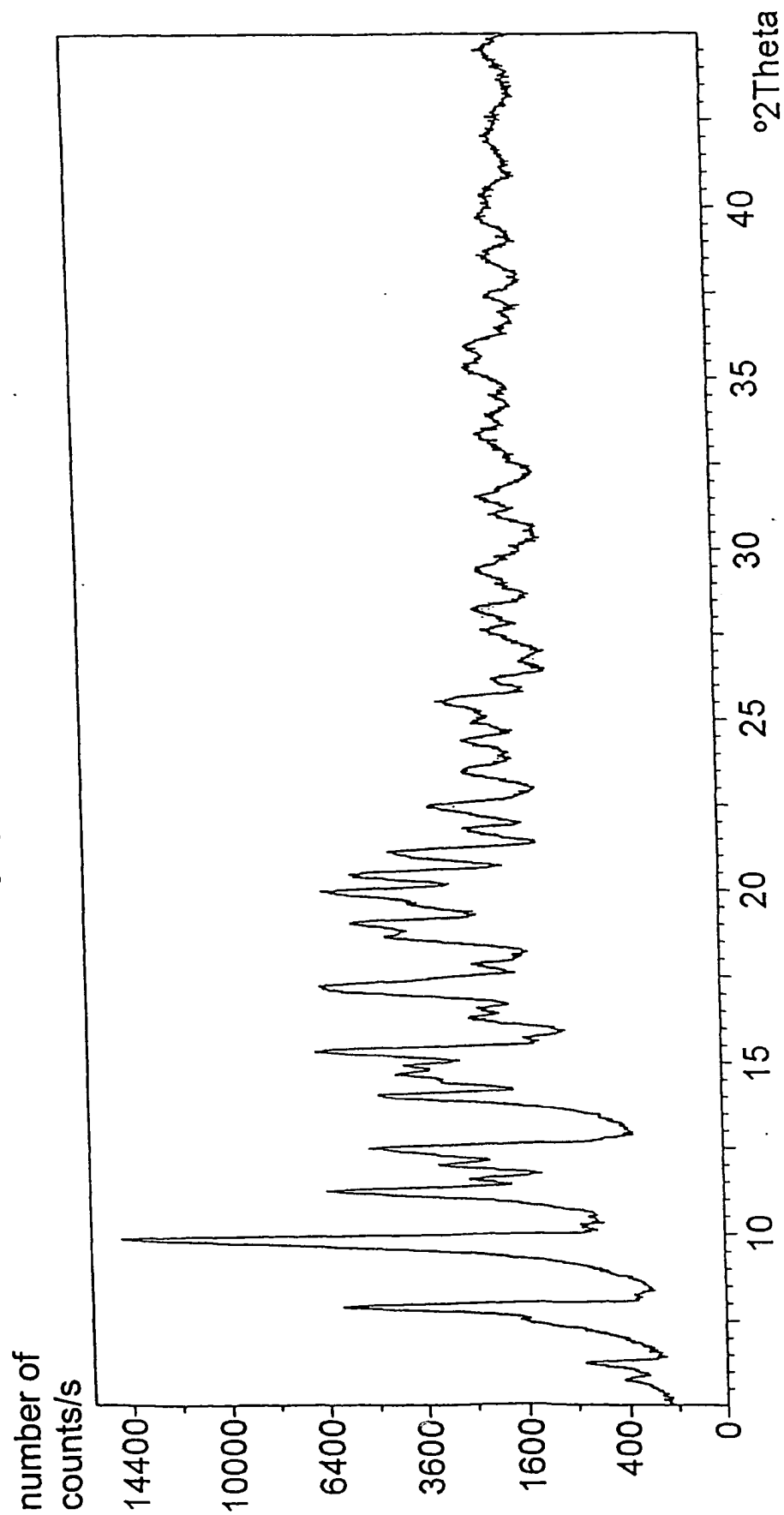
11. Pharmaceutical composition that includes a therapeutically effective quantity of improved form of azitromycin monohydrate as claimed in any of Claims 1 to 6 in association with at least one pharmaceutically
30 acceptable suitable inert diluent.

12. Method for preparation of the pharmaceutical composition claimed in Claim 11, characterised in that it combines the azitromycin monohydrate of lower
35 hygroscopicity with at least one pharmaceutically

acceptable suitable inert diluent, administered orally and parenterally.

1/4

FIG. 1



2/4

FIG. 2

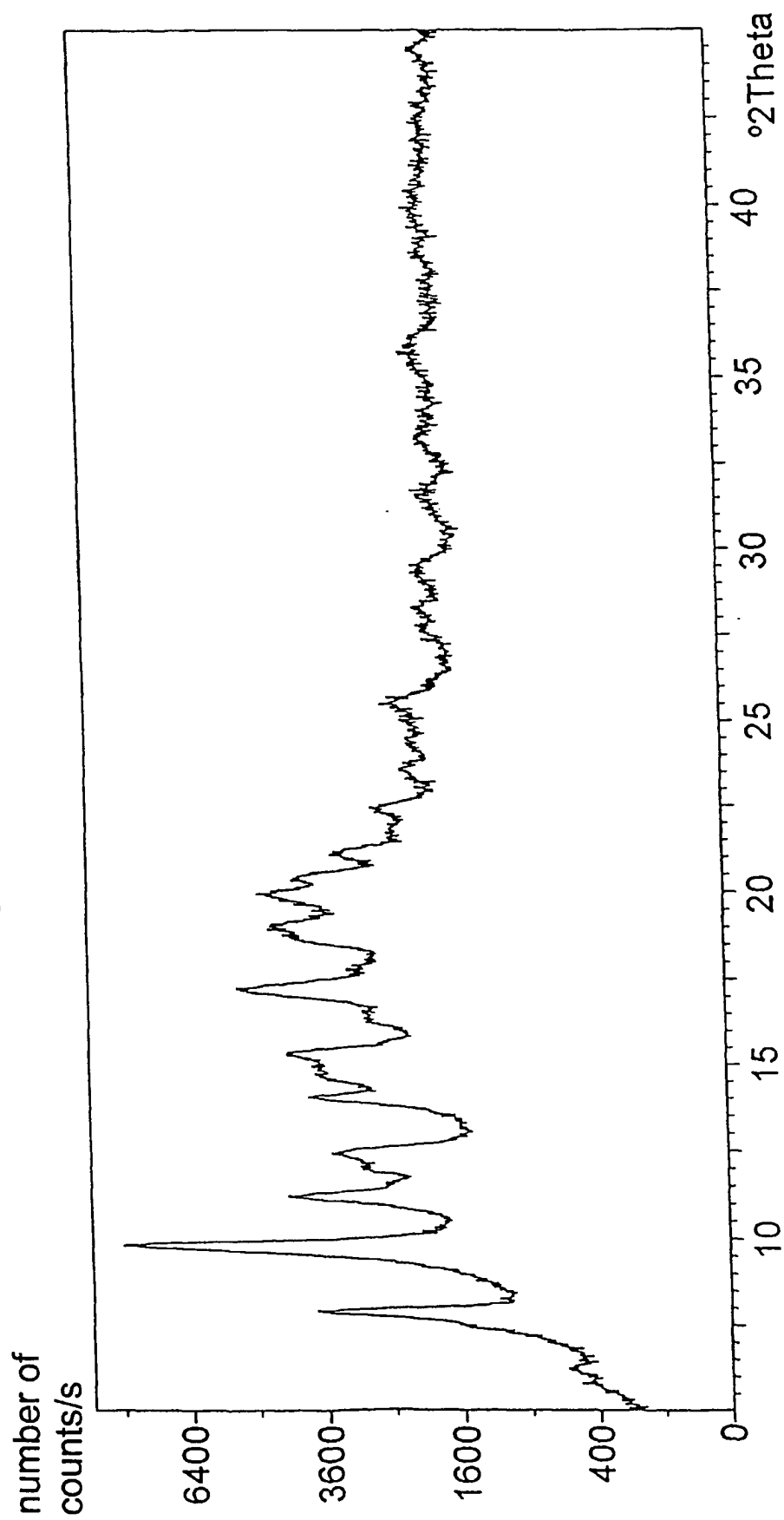
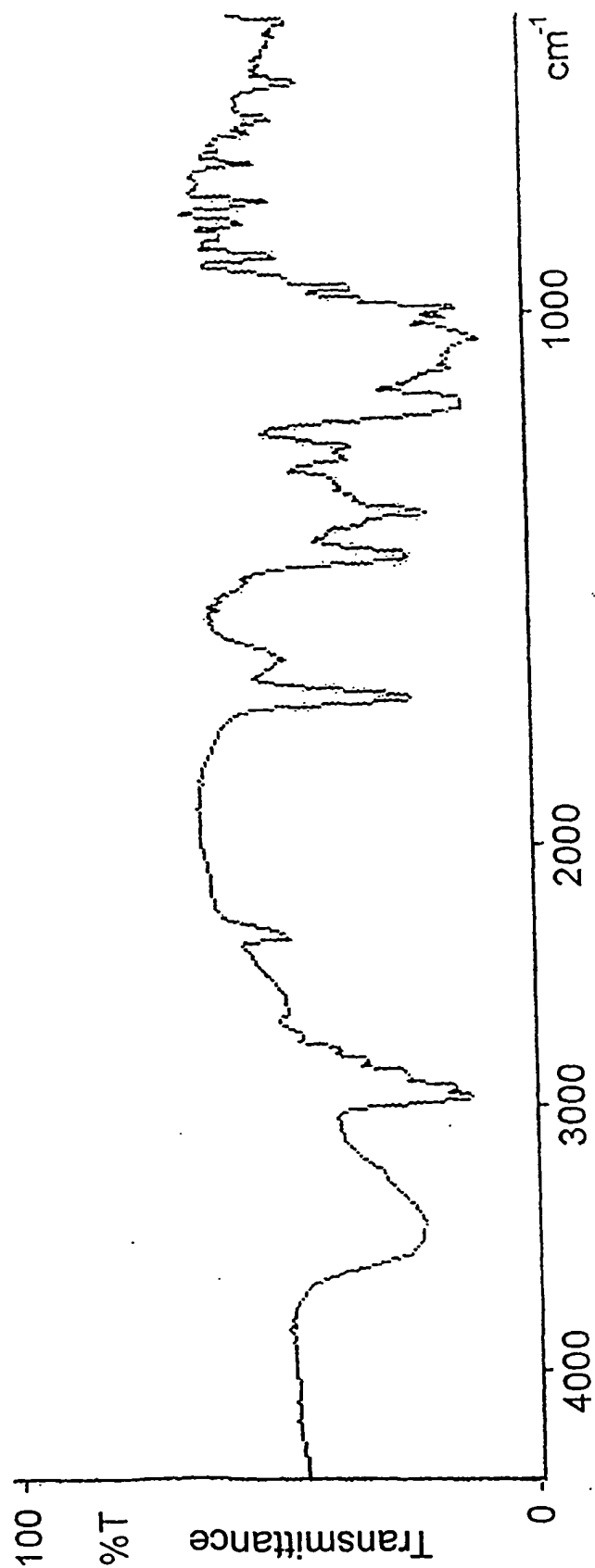
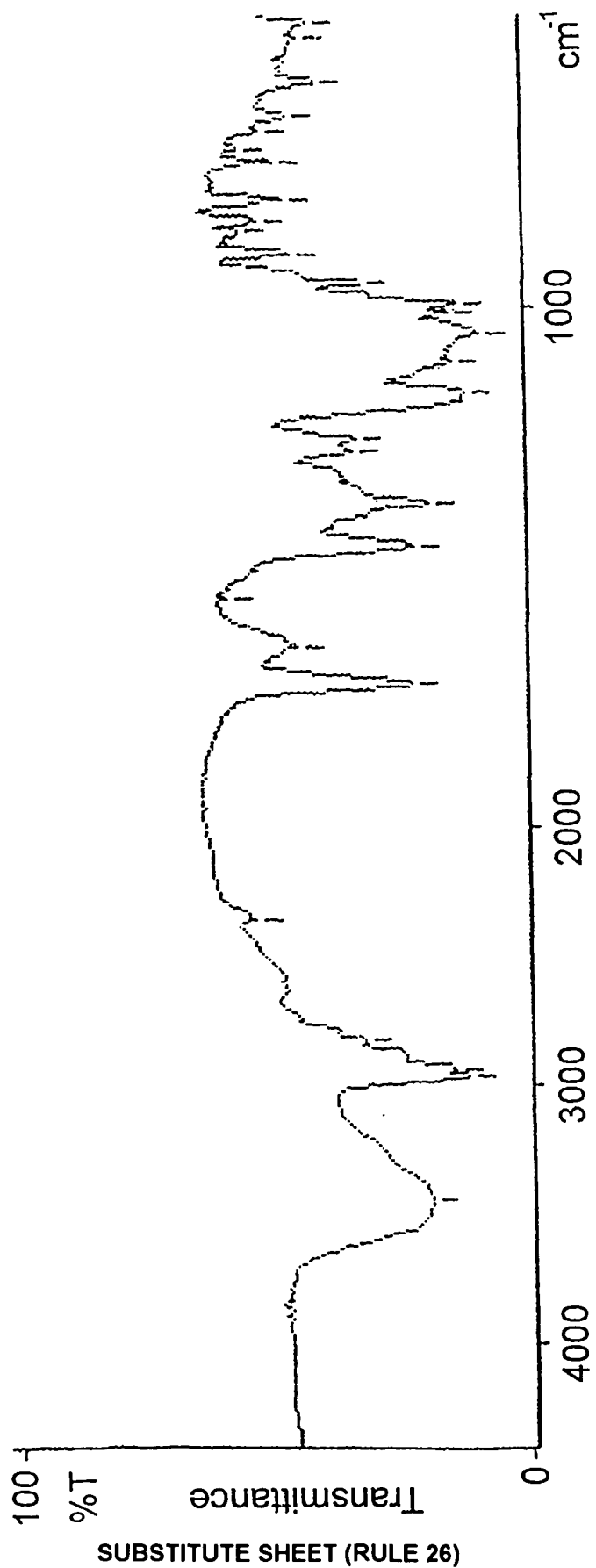


FIG. 3



4 / 4

FIG. 4



INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/IB 01/01327

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H17/08 A61K31/7052 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 298 650 A (PFIZER) 11 January 1989 (1989-01-11) cited in the application the whole document	1
P,X	WO 01 00640 A (LUDESCHER JOHANNES ; GARCIA RAFAEL (ES); BIOCHEMIE SA (ES); DIAGO J) 4 January 2001 (2001-01-04) abstract claims	1,10-12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

5 September 2001

Date of mailing of the international search report

19/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

de Nooy, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/01327

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0298650 A	11-01-1989	WO 8900576 A	26-01-1989
		AP 44 A	27-07-1989
		AT 72446 T	15-02-1992
		AU 604553 B	20-12-1990
		AU 1883988 A	12-01-1989
		BA 98213 B	02-08-1999
		BG 47348 A	15-06-1990
		CA 1314876 A	23-03-1993
		CN 1030422 A,B	18-01-1989
		CS 8804896 A	14-03-1990
		CY 1776 A	20-10-1995
		DD 271705 A	13-09-1989
		DE 3868296 A	19-03-1992
		DK 380688 A	10-01-1989
		ES 2038756 T	01-08-1993
		FI 900087 A,B,	08-01-1990
		GR 3003737 T	16-03-1993
		HK 127594 A	25-11-1994
		HU 9500738 A	28-11-1995
		IE 60354 B	29-06-1994
		IL 86979 A	15-11-1992
		IN 168879 A	29-06-1991
		JP 1038096 A	08-02-1989
		JP 1903527 C	08-02-1995
		JP 6031300 B	27-04-1994
		KR 9006218 B	25-08-1990
		LV 10624 A	20-04-1995
		MX 12213 A	01-05-1993
		NZ 225338 A	26-02-1990
		OA 8743 A	31-03-1989
		PT 87933 A,B	30-06-1989
		RO 107257 B	30-10-1993
		SG 27794 G	14-10-1994
		SI 8811325 A	31-12-1996
		RU 2066324 C	10-09-1996
		US 6268489 B	31-07-2001
		YU 132588 A	28-02-1990
		ZA 8804925 A	28-02-1990
WO 0100640 A	04-01-2001	AU 5820400 A	31-01-2001

